INTRAVENOUS PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING THE SAME

The present invention relates to an intravenous pharmaceutical composition comprising cyclosporin as active ingredient. Furthermore the invention relates to a process for preparing this composition.

Cyclosporins are cyclic oligopeptides produced by microorganisms. Cyclosporin A, C and G exhibit significant immunosuppressive effect. Cyclosporin A is widely used when organs (kidney, heart, lungs, liver, pancreas) are transplanted in order to inhibit the rejection provoked by the transplanted organ and when bone marrow is transplanted cyclosporin A is given to prevent graft-versus-host disease. Cyclosporin A is also successfully used for the treatment of Autoimmune disorders (e.g. diabetes juvenilis, rheumatoid arthritis, uveitis, psoriasis).

Cyclosporins are formed from neutral amino acids of hydrophobic character and are insoluble in water. Their poor solubility in water causes that they are not absorbed or only partly absorbed in the organism when administered together with usual pharmaceutical excipients, therefore these compositions are not suitable for therapeutical use.

Cyclosporins have to be dissolved or dispersed in a colloid system if they are aimed to be used in therapeutical practice.

In order to make cyclosporins usable in therapy, the following solutions were worked out:

1. So-called "solid solutions" are prepared by using polyethylene glycols of high molar mass (Chion, W. L., Riegelman, S.: J. Pharm. Sci. 60, 1281 /1971/).

2. Cyclosporin is dissolved in natural oils and the solution thus obtained is encapsulated (van Hoff, J. P. et al.: 1987, II. 1456).

3. Cyclosporin is dissolved in the mixture of a trans esterification product of a natural vegetable oil triglyceride, a polyalkylene glycol, ethanol and a vegetable oil (Austrian patent specification No. 375,828, U.S. Pat. No. 4,388,307).

4/ Cyclosporin is dissolved in a mixture of ethanol and CREMOPHOR EL (polyoxyethylated castor oil, produced by BASF, Ludwigshafen, Germany) (Sandimmun Product Information, Chapter XII, Sandoz-Pharma, Basle, 1984).

The products prepared according to method 1 are not suitable for parenteral use, they are pellet particles which can be administered orally.

The products prepared according to method 2 are also suitable for oral administration only.

The products prepared according to method 3 are not suitable for intravenous administration due to their oil content, therefore they can be used subcutaneously or intramuscularly.

The intravenous administration of compositions prepared according to method 4 is well known in the art. However, they suffer from the drawback that they are not well-tolerable by the patients, i.e. after administration they often cause anaphylactic reactions which are dangerous from the point of view of the patient (Kahan et al.: Lancet, 1984, I:52; Leunissen, K. M. L. et al.: Lancet, 1985, I:636; Howrie, D. L. et al.: Drug Intell. Clin. Pharm. 19 425 /1985/).

The anaphylactic reaction does not occur when cyclosporin is administered in different compositions, therefore it has been stated that the polyoxyethylated castor oil is exclusively responsible for causing the anaphylactic reaction (CREMOHPOR EL, Technical Leaflet MEF 074e, BASF, Ludwigshafen, 1984). Though the activity of CREMOPHOR was thoroughly studied, there is no literary reference teaching the moiety of the molecule which is responsible for the dangerous side-effect.

Therefore our aim was to work out an intravenous pharmaceutical composition comprising cyclosporin as active ingredient which is more tolerable than the known intravenous formulations, i.e. its anaphylactic-hypersenzibilizing effect is smaller than that of the known formulation.

Now we have found that if cyclosporin is dissolved in the mixture of an alcohol suitable for intravenous administration and a monoester of a saturated hydroxylated fatty acid formed with polyethylene glycol, the occurrence and extent of the toxic side-effects can significantly be decreased or fully eliminated.

As the monoesters of saturated hydroxylated fatty acids formed with polyethylene glycol are structurally similar to CREMOPHOR, it could not be expected by a man skilled in the art that the occurrence of the toxic side-effects can be overcome by using these compounds.

The intravenous pharmaceutical composition containing cyclosporin as active ingredient of the present invention comprises

a) 1 part by mass of one or more cyclosporins,
b) 8 to 13 parts by mass of a monoester of a saturated hydroxylated fatty acid formed with polyethylene glycol on the mixture of such monoesters,
c) 4 to 10 parts by mass of one or more intravenously administerable mono- or polyvalent alcohols.

The composition according to the invention is prepared by mixing

a) 1 part by mass of one or more cyclosporins,
b) 8 to 13 parts by mass of a monoester of a saturated hydroxylated fatty acid formed with polyethylene glycol or the mixture of such monoesters,
c) 4 to 10 parts by mass of one or more intravenously administerable mono- or polyvalent alcohols.

The pharmaceutical compositions according to the invention are suitable for the intravenous administration of the hydrophobic cyclosporin A, G, C or the mixture thereof which are insoluble or poorly soluble in the usual pharmaceutical excipients and enable the administration of the said cyclosporins in an aqueous solution. The cyclosporins can be used in any mass ratio related to each other in the composition of the invention.

As components b) of the pharmaceutical composition according to the invention, the monoesters of C_{10-22} preferably C_{14-22}, more preferably C_{16-20} saturated hydroxylated fatty acids formed with polyethylene glycol (PEG) of a molar weight of 600 to 1300, preferably 750 to 1100 or the mixture of such monoesters of any mass ratio can be used. Especially preferred monoesters are PEG-9-hydroxymiristate, PEG-9-hydroxypalmitate and PEG-12-hydroxystearate wherein the PEG moiety has a molar weight of 750 to 1150, or the mixtures thereof in any mass ratio.

These compounds can be prepared e.g. by the method of Chandrasekhara Rao, T. et al. (J. Am. Oil Chem. Soc., 54, 18, /1977/). Polyethylene glycol-12-hydroxystearate is commercially available. These components b) can dissolve the hydrophobic cyclosporins in the presence of co-solvents even at room temperature.